Procedure to Measure the Quantity of Nicotine Contained in Cigarette Filler utilized by Philip Morris Incorporated, based on a variant of the "Protocol to Measure the Quantity of Nicotine Contained in Smokeless Tobacco Products Manufactured, Imported, or Packaged in the United States," published in the Federal Register on May 2, 1997, Vol. 62, No. 85, pp. 24115-24116

Key to Revisions:

Deletions - strike-through
Additions - Bold and underlined

FEDERAL REGISTER
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Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
Public Health Service (PHS)
Centers for Disease Control (CDC)

Protocol to Measure the Quantity of Nicotine Contained in Smokeless Tobacco Products Manufactured, Imported, or Packaged in the United States

62 FR 24116

DATE: Friday, May 2, 1997

ACTION: Request for comments.

SUMMARY: CDC's Office on Smoking and Health (OSH) is requesting comments from all interested parties on a standard methodology for measurement of quantity of nicotine in smokeless tobacco. The Comprehensive Smokeless Tobacco Health Education Act of 1986 (15 U.S.C. 4401 et seq., Pub. L. 99-252) requires that each person who manufactures, packages, or imports smokeless tobacco provide the Secretary of HHS annually with a report on the quantity of nicotine contained in smokeless tobacco products; OSH has been delegated the authority to implement the nicotine reporting provisions of this law. The methodology ("Protocol for Analysis of Nicotine, Total Moisture, and pH in Smokeless Tobacco Products") is the basis for such nicotine reporting and is intended to provide standardized measurement of nicotine, total moisture, and pH in smokeless tobacco products.

Source: https://www.industrydocuments.ucsf.edu/docs/sydl0001

DATES: Written comments to this notice should be submitted to Patricia Richter, Centers for Disease Control and Prevention (CDC), Office on Smoking and Health, 4770 Buford Highway, NE., Mailstop K50, Atlanta, Georgia 30341-3724 on or before June 2, 1997. Comments may also be faxed to Patricia Richter at (770) 488-5848 or submitted by email to pir1@cdc.gov as WordPerfect 5.0, 5.1/5.2, 6.0/6.1 or
ASCII files.

FOR FURTHER INFORMATION CONTACT: Patricia Richter, Centers for Disease Control and Prevention (CDC), Office on Smoking and Health, 4770 Buford Highway NE., Mailstop K50, Atlanta, Georgia 30341-3724; telephone: (770) 488-5703.

SUPPLEMENTARY INFORMATION: In 1989, the smokeless tobacco industry submitted a business review letter to the Department of Justice (DOJ), in accordance with 28
CFR 50.6. This letter requested approval of a collaborative industry effort to determine standard nicotine reporting. Previous to this, each company employed different methods of nicotine and moisture analysis; however, HHS requested that a standard methodology be developed to ensure the accuracy and reliability of the information on nicotine and moisture, as well as to ensure comparability of the data. HHS did not have the resources to develop such a standardized methodology thus necessitating a collaborative industry process to develop the methodology.

In January 1993, DOJ extended permission to the smokeless industry to begin the development of uniform methods for analyzing smokeless tobacco products for nicotine and moisture content. The smokeless tobacco industry formed a work group, which represented the ten major domestic manufacturers of smokeless tobacco. The first meeting of the work group was on July 7, 1993 and the group continued to meet throughout 1993 and 1994. After this series of meetings, a standard methodology was approved by the work group and submitted to OSH. The protocol was revised by OSH based on individual comments received from peer reviewers and the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, CDC. Once OSH has received comments, it will review the comments, make the necessary changes to the methodology, and publish the final methodology in the Federal Register. Once the final methodology has been published, OSH will implement the nicotine reporting requirements of the
Act.

Dated: April 24, 1997.

Joseph R. Carter,

Acting Associate Director for Management and Operations, Centers for Disease Control and Prevention (CDC).

Source: https://www.industrydocuments.ucsf.edu/docs/sydl0001

Standardized methodology: Protocol for Analysis of Nicotine, Total Moisture, and pH in Smokeless Tobacco Products

I. Requirements[1,2]

A. Reagents[3]

1. 2 N Sodium hydroxide (NaOH)
2. Methyl t-butyl ether (MTBE)
3. (-)-Nicotine (Fluka 72290) >99% purity [4]
4. Quinoline (Aldrich)
5. ~~Standard pH buffers; 7.00 and 10.00~~
6. Deionized distilled water

B. Glassware and supplies

1. Volumetric flasks
2. 25 mm x 200 mm Pyrex culture tubes with Teflon lined screw caps (Mfr #982625X)
3. Pasteur pipettes
4. Repipettors (10 mL and 50 mL)
5. Linear shaker (configured to hold tubes in horizontal position) [5,6]
6. Moisture dish-Al, diam. 45-65 mm, depth 20-45 mm, with tight fitting cover
7. Teflon-coated magnetic stirring bar
8. ~~50 mL polypropylene container~~

C. Instrumentation

1. Robot Coupe Model RSI 6V Scientific Batch Processor or equivalent
2. Capillary gas chromatograph with modified split capability (splitless/split), flame ionization detector, integrator, a 4 mm

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split/splitless glass liner and a 30 m x 0.32 mm ID fused silica column crosslinked and coated with 5% phenyl and 95% methyl silicone at 1 m film thickness.

3. ~~Orion Model SA 720 pH meter equipped with Orion 8103 Ross Combination pH electrode.~~

D. Additional Equipment

~~Forced draft oven, regulated to 99.5 # 0.5 °C. Suggested dimensions: 19x19x19" (48 cm). Approx. oven settings: fresh air intake vent 1/5 open; air control damper 1/4 open; air exhaust vent 1/3 open.~~

E. Chromatographic Conditions [7,8]

1. Detector temperature: 250 °C

2. Injector temperature: 250 °C

3. Flow rate at 100 °C-1.7 mL/min; with split ratio of 40:1 [9]

4. Injection volume: 2 µl

5. Column conditions: 110-185 ^{0}C at 10 ^{0} C min-1; 185-240 ^{0} C at 6 ^{0} C min $^{-1}$, hold at final temperature for 10 min. Equil. time: 5 min.

F. Sample Preparation [10]

There exist six different categories of commercial smokeless tobacco products:

~~1. Dry snuff;~~

~~2. Wet snuff;~~

~~3. Wet snuff portion packs;~~

~~4. Plug;~~

~~5. Twist; and~~

~~6. Loose leaf.~~

7. **Cigarette Filler**

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Because of their physical characteristics, samples of three of the six product categories must be ground before nicotine, ~~total moisture, and pH~~ analyses can be conducted. The objective of grinding the samples is to obtain a homogeneous sample with particles measuring approximately 4 mm. Grinding to achieve this particle size should take no more than 3 minutes. To ensure proper grinding and an adequate amount of the ground sample for analysis, the minimum sample size of all commercial products to be ground should not be less than 100 grams.

To ensure precision of analyses for nicotine, ~~total moisture, and pH~~, the samples that require grinding should be ground using a Robot Coupe Model RSI 6V Scientific Batch Processor or its equivalent. This is a variable speed (0 to 3000 RPM) processor. The variable speed motor is required to ensure proper grinding of the tobacco tissues ~~(and in the case of pH determination, the wet snuff portion pack)~~. Elevated temperatures can result in moisture loss and an underestimated value for moisture content. Hence, care must be taken during grinding to avoid elevated temperatures. The bowl should be cleaned after each grinding to obtain accurate results.

~~1. Dry snuff. Dry snuff samples do not need to be ground since the product is a powder. The sample must be thoroughly mixed before weighing for nicotine, total moisture, and pH analysis.~~

~~2. Wet snuff. Wet snuff samples do not need to be ground. The sample must be thoroughly mixed before weighing for nicotine, total moisture, and pH analysis.~~

~~3. Wet snuff portion packs. The tobacco contents of the wet snuff portion packs do not need to be ground for nicotine, total moisture, or pH analysis. The tobacco packaging material (the "pouch") should be separated from the tobacco and ground to obtain particles measuring approximately 4 mm for pH analysis. The tobacco of the wet snuff portion pack and the ground pouch are combined and thoroughly mixed before pH analysis.~~

~~4. Plug tobacco. Break or cut apart plugs and add in portions to grinder at 2000 RPM. Reduce RPM or stop grinding if sample bowl becomes warm. Pulse the Robot Coupe, when needed, to complete grinding. Grind samples until approximately 4 mm in size. The total grinding time should be no more than 3 minutes.~~

~~5. Twist tobacco. Separate twists, add to grinder and grind at 2000 RPM. Reduce RPM or stop grinding if sample bowl becomes warm. Continue grinding until sample particles are approximately 4 mm in size. The total time for grinding should be no more than 3 minutes.~~

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~~6. Loose-leaf. Grind in the same manner as described in 4 and 5 to obtain product with particle size of approximately 4 mm.~~

7. Cigarette Filler. Add at least 100 grams of filler to the bowl of the Robot Coupe RSI 6V and process at 2000 rpm for 3 minutes. Immediately transfer the filler to a quart glass jar and close.

II. Nicotine Analysis

A. Calibration Standards

1. Internal Standard (IS)

Weigh 10.00 grams of quinoline, transfer to a 250 mL volumetric flask and dilute to volume with MTBE. This solution will be used for calibration of the instrument for the nicotine calibration curve (II.A.2), for the standards addition assay (II.B), and for preparation of the extracting solution (II.D).

2. Nicotine Calibration Curve
   a. Weigh 1.0000 gram of nicotine into a clean, dry 100 mL volumetric flask and dilute to volume with MTBE. This gives a nicotine concentration of 10 mg/mL for the stock solution. **Weigh 1.000 + 0.0020 grams and record exact weight.**
   b. Accurately pipette 0.5 mL of IS from stock solution (II.A.1) to five clean, dry 50 mL volumetric flasks. To prepare a nicotine standard corresponding to a concentration of 0.8 mg/mL, pipette exactly 4.0 mL of the nicotine standard (II.A.2.a) to a 50 mL volumetric flask containing the internal standard and dilute to volume with MTBE. To obtain nicotine concentrations equivalent to 0.6, 0.4, 0.2, and 0.1 mg/mL, pipette precisely 3.0, 2.0, 1.0, and 0.5 mL, respectively, of the nicotine standard into the four remaining flasks and dilute to volume with MTBE. **Calculate exact concentration of nicotine from the exact concentration of the stock solution.**
   c. Transfer aliquots of the five standards to auto sampler vials and determine the detector response for each standard using gas chromatographic conditions described in I.E.

   d. Calculate least squares line for linear equation from these standards by obtaining the ratio of Area[nicotine]/Area[IS]. This ratio will be the Y value and the concentration of nicotine will be the X value for determining the linear equation of the line (Equation 1):

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Equation 1:

$Y = a+bX;$

Where:

X = Concentration of nicotine in mg

Y = Area[nicotine]/Area[IS]

a = I ntercept on the ordinate (y axis)

b = slope of the curve

~~The final result will be reported in the following units:~~
The result from the laboratory data system will be reported in the following units:

Weight % Nicotine = (gram of nicotine/gram of tobacco sample) x 100

e. Determine the recovery of nicotine by pipetting 10 mL of the 0.4 mg/mL nicotine standard to a screw capped tube containing 1.0 mL of 2 N NaOH. Cap the tube. Shake the contents vigorously and allow the phases to separate. Transfer an aliquot of the organic phase to an injection vial and inject. Calculate the concentration of nicotine using the equation of the line in II.A.2.d above. This should be repeated two more times to obtain an average of the three values. The recovery of nicotine can be obtained by using the following equation:

Equation 2:

Recovery = Nicotine[calculated]/Nicotine[actual]

B. Standards Addition Assay

Prior to analyzing a smokeless tobacco product for nicotine content, the testing facility must validate the system to verify that matrix bias is not occurring during nicotine extraction. This is done by analyzing the nicotine calibration standards in the same vegetable matrix as the smokeless tobacco. The standards addition assay should be performed with ***cigarette filler from each individual brand*** tested.

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1. Using an analytical balance, accurately weigh 1.000 # 0.020 gram of the homogeneous, prepared tobacco sample into a culture tube. Repeat this five times for a total of 6 culture tubes containing the smokeless tobacco product. Record the weight of each sample.

2. To prepare a nicotine standard corresponding to a concentration of 0.8 mg/mL, pipette exactly 4.4 mL of the nicotine standard (II.A.2.a) to one of the culture tubes. To obtain nicotine concentrations equivalent to 0.6, 0.4, 0.2, and 0.1 mg/mL, pipette precisely 3.3, 2.2, 1.1, and 0.55 mL, respectively, of the nicotine standard into four of the remaining culture tubes. One of the culture tubes is not supplemented with nicotine and serves as an analytical blank. Allow the samples to equilibrate for 10 minutes.

3. Pipette 5 mL of 2 N NaOH into each tube. Cap each tube. Swirl to wet sample and allow to stand 15 minutes. [11]

4. Pipette 50 mL of extraction solution (II.D.1) into each tube. Cap each tube and tighten. [12]

5. Place tubes in rack(s), place racks in linear shaker in horizontal position and shake for two hours.

6. Remove rack(s) from shaker and place in vertical position to allow the phases to separate.

7. Allow the solvent and nicotine supplemented samples and the blank to separate (maximum 2 hours).

8. Transfer aliquots of the five standards and the blank from the extraction tubes to sample vials and determine the detector response for each using gas chromatographic conditions described in I.E.

9. Subtract the Area[nicotine]/Area[IS] of the blank from the Area[nicotine]/Area[IS] of each of the standards.

10. Calculate least squares line for linear equation from the corrected standards as described above (Equation 1) in II.A.2.d.

    The final corrected result will be reported in the following units:

    Concentration of nicotine = mg of nicotine/gram of tobacco sample.

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11. Determine the recovery of nicotine by pipetting 10 mL of the 0.4 mg/mL nicotine standard to a screw capped tube containing 1.0 mL of 2 N NaOH and 10 mL of extraction solution (II.D.1). Cap the tube and tighten. Shake the contents vigorously and allow the phases to separate. Transfer an aliquot of the organic phase to an injection vial and inject. Calculate the concentration of nicotine using the equation of the line above in II.A.2.d. This should be repeated two more times to obtain an average of the three values. The recovery of nicotine can be obtained by using Equation 2:

    Recovery = Nicotine[calculated]/Nicotine[actual]

12. **Recoveries were performed on each individual cigarette brand and average correction factor for that product was applied to the result generated using a nicotine calibration curve in an aqueous matrix..**

C. Quality Control Pool

At least two quality control pools prepared in the smokeless tobacco product matrix are recommended to be included in each analytical run. ~~The smokeless tobacco product should be enriched with nicotine at the high and low ends of expected values for the smokeless tobacco product~~. The pools must be analyzed in duplicate in every run. The quality control pool must be prepared in sufficient quantity to last for all analyses of a product lot.
Two tobaccos selected to contain nicotine higher and lower than the expected samples were prepared using the Robot Coupe Model RSI 6V scientific Batch Processor as described in I.F.7. These two quality control pools were included in each analytical run.

D. Sample Extraction Procedure

1. Extraction solution is prepared by pipetting 10 mL of the IS from the stock solution (II.A.1) to a 1000 mL volumetric flask and diluting to volume with MTBE.

2. Using an analytical balance, accurately weigh 1.000 $\pm$ 0.020 gram of prepared tobacco sample into culture tube and record weight. [13] The number of products sampled per lot should reflect an acceptable level of precision. [14] The test material is to be representative of the product that is sold to the public and therefore should consist of sealed, packaged samples from each lot of finished product that is ready for commercial distribution.

    Triplicate determinations will provide precision data.

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3. Pipette 5 mL of 2 N NaOH into the tube. Cap the tube. Swirl to wet sample and allow to stand 15 minutes. [11]

4. Pipette 50 mL of extraction solution into tube, cap tube and tighten. [12]

5. Place tubes in rack(s), place racks in linear shaker in horizontal position and shake for two hours.

6. Remove rack(s) from shaker and place in vertical position to allow the phases to separate.

7. Allow the solvent and sample to separate (maximum 2 hours). Transfer an aliquot from the extraction tube to a sample vial and cap.

8. Analyze the extract using GC conditions as described above (I.E) and calculate the concentration of nicotine using the linear calibration equation. Correct percent nicotine values for both recovery and weight of sample by using Equation 3. [15]

Equation 3: [16]

$$\text{Nicotine (mg/g)} = \frac{(\text{Area}_{\text{nicotine}}/\text{Area}_{\text{IS}}) - a}{b \times \text{Sample Wt} \times \text{Recovery}}$$

~~9. Report the final nicotine determination as mg of nicotine per gram of the tobacco product (mg nicotine/gram), to an accuracy level of two decimal places. All data should include the mean value with a 95% confidence interval, the range of values, the number of samples tested per lot, and the estimated precision of the mean. Information will be reported for each manufacturer and variety (including brand families and brand variations) and brand name (e.g., Skoal Bandits, Skoal Long Cut Cherry, Skoal Long Cut Wintergreen, etc.).~~

Report the final nicotine determination as mg of nicotine per cigarette to an accuracy of two decimal places. All data should include the mean value with a 95% confidence interval, the range of values, the number of replicates per brand.

$$\text{Mg Nicotine per Cigarette} = \frac{\text{Wt \% Nicotine (Corrected for Recovery)}}{100} \times \text{Average Weight (g) filler per cigarette} \times 1000$$

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Note - Sections III ("Total Moisture Determination") and IV. ("pH Measurement") were not utilzed, consistent with Section 660.102(B)(2) of the CMR

V. Assay Criteria for Quality Assurance

A. Establishing limits for Quality Control Parameters

All quality control parameters must be determined within the laboratory in which they are to be used. At least 10 within-laboratory runs must be performed to establish temporary confidence intervals for the quality control parameters. Permanent limits should be established after 20 runs and should be reestablished after each additional 20 runs.

B. Exclusion of Outliers from the Calibration Curve [16]

The coefficient of determination between Area[nicotine]/Area[IS] and nicotine concentration should be equal to 0.99 or higher. Any calibration standard having an estimated concentration computed from the regression equation (Equation 1) which is different from its actual concentration by a factor of 10% can be excluded from the calibration curve. Up to two concentrations may be excluded, but caution should be used in eliminating values, since bias may be increased in the calibration curve. If an outlier value is eliminated, its duplicate value must also be discarded to avoid producing a new bias. All unknowns must fall within the calibration curve; therefore, duplicate values excluded at either end of the calibration curve will restrict the useful range of the assay.

C. Quality Control Pools and Run Rejection Rules

The mean estimated nicotine concentration in a pool should be compared with the established limits for that pool based on at least 20 consecutive runs. An analytical run should be accepted or rejected based upon the following set of rules adapted from Westgard et al. (1981).

1. When the mean of one QC pool exceeds the limit of $x \pm 3$ standard deviations (SD), then the run is rejected as out of control. Here, x and SD represent the overall mean and standard deviation of all estimated nicotine concentrations for a particular pool in the runs which were used to establish the control limits.

2. When the mean nicotine concentrations in two QC pools in the same run exceed the same direction, then the run must be rejected. The same

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direction is the condition in which both pools exceed either the x + 2 SD or the x-2 SD limits.

3. When the mean nicotine concentrations in one or two QC pools exceed their x + 2 SD limits in the same direction in two consecutive runs, then both runs must be rejected.

4. When the mean nicotine concentrations in two QC pools are different by more than a total of 4 SD, then the run must be rejected. This condition may occur, for example, when one QC pool is 2 SD greater than the mean, and another is 2 SD less than the mean.

Endnotes

The comments and notes listed below can be described as Good Laboratory Practice guidelines; they are described in detail in this protocol to ensure minimal interlaboratory variability in the determination of nicotine, total moisture, and pH in smokeless tobacco.

[1]This protocol assumes that the testing facility will implement and maintain a stringent Quality Assurance/Quality Control program to include, but not be limited to, regular interlaboratory comparisons, routine testing of random blank samples, determination of the quality and purity of purchased products, and proper storage and handling of all reagents and samples.

[2]When a specific product or instrument is listed, it is the product or instrument that was used in the development of this method. Equivalent products or instruments may also be used. The use of company or product name(s) is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention.

[3]All chemicals, solvents, and gases are to be of the highest purity.

[4]Companies must ensure that the purity of the nicotine base is certified by the vendor and that the chemical is properly stored. However, nicotine base oxidizes with storage, as reflected by the liquid turning brown. If oxidation has occurred, the nicotine base should be distilled prior to use in making a standard solution.

[5]Horizontal shaking will allow more intimate contact of this three phase extraction. There is a minimal dead volume in the tube due to the large sample size and extraction volume. This necessitates horizontal shaking.

6If linear shaker is not available, a wrist action shaker using 250 mL stoppered Erlenmeyer flasks can be substituted. Values for nicotine are equivalent to those obtained from the linear shaker.

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[7]After installing a new column, condition the column by injecting a tobacco sample extract on the column, using the described column conditions. Injections should be repeated until areas of IS and nicotine are reproducible. This will require approximately four injections. Recondition column when instrument has been used infrequently and after replacing glass liner.

[8]Glass liner and septum should be replaced after every 100 injections.

[9]Most older instruments operate at constant pressure. To reduce confusion, it is suggested that the carrier gas flow through the column be measured at the initial column temperature.

[10]The testing facility must ensure that samples are obtained through the use of a survey design protocol for sampling "at one point in time" at the factory or warehouse. The survey design protocol must address short-, medium-and long-term product variability (e.g., variability over time and from container to container of the tobacco product) as defined by ISO Protocol 8243, Annex C. Information accompanying results for each sample should include, but not be limited to:

1. For each product-manufacturer and variety (including brand families and brand variations) and brand name (e.g., Skoal Bandits, Skoal Long Cut Cherry, Skoal Long Cut Wintergreen, etc.) information.

2. Product "category," e.g., loose leaf, plug, twist, dry snuff, moist snuff, **cigarettes** etc.

3. Lot number.

4. Lot size.

5. Number of randomly sampled, sealed, packaged (so as to be representative of the product that is sold to the public) smokeless tobacco products selected per lot (sampling fraction) for nicotine, moisture, and pH determination.

6. Documentation of method used for random sample selection.

7. "Age" of product when received by testing facility and storage conditions prior to analysis.

[11]Use non-glass 10 mL repipette for transferring NaOH solution.

[12]Use 50 mL repipette for transferring MTBE.

[13]For dry snuff, use 0.500 # 0.010 gram sample.

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[14]The testing facility is referred to ISO Procedure 8243 for a discussion of sample size and the effect of variability on the precision of the mean of the sample (ISO 8243, 1991).

[15]When analyzing new smokeless tobacco products, extract product without IS to determine if any components co-elute with the IS or impurities in the IS. This interference could artificially lower calculated values for nicotine.

[16]The calculated nicotine values for all samples must fall within the low and high nicotine values used for the calibration curve. If not, prepare a fresh nicotine standard solution and an appropriate series of standard nicotine dilutions. Determine the detector response for each standard using chromatographic conditions described in I.E.

[17]The method is a modification of AOAC Method 966.02 (1990) in that the ground tobacco passes through a 4 mm screen rather than a 1 mm screen.

[18]When drying samples, do not dry different products (e.g., wet snuff, dry snuff, loose leaf) in the oven at the same time since this will produce errors in the moisture determinations.

References

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